09.2020

Ultomiris

אולטומיריס

Active ingredient:

RAVULIZUMAB

חומר פעיל:

רבוליזומאב

Concentrate for solution for infusion
IV

תרכיז להכנת תמיסה לעירוי
תוך ורידי

רופא/ה, רוקח/ת נכבד/ה,
העלון לרופא של המוצר עודכן בספטמבר 2020 וזאת **לאחר קבלת אישור עבור התוויה חדשה:**
atypical haemolytic Uremic syndrome (aHUS)

העלון מכיל בתוכו עדכונים רבים בפרקים שונים. מובאים להלן בצהוב רק העדכונים העיקריים הנוגעים להתוויה החדשה וההשלכות שלה על פרק משטר המינון, ועדכוני הבטיחות.
בעלון ניתן למצוא מידע נוסף חדש מתוך המחקר הקליני בפרקים הנוספים של העלון אשר אינם מובאים בהודעה זו.

נוסח ההתוויה המאושר לתכשיר כפי שמופיע ברישיון התכשיר:

ULTOMIRIS is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):
•in patients with haemolysis with clinical symptom(s) indicative of high disease activity
•in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.

Ultomiris is indicated in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic Uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

העדכונים בעלון לרופא הנוגעים להתוויה, משטר מינון ובטיחות:

4.1 Therapeutic indications

Patient safety information card
The marketing of Ultomiris is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):
- in patients with haemolysis with clinical symptom(s) indicative of high disease activity
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section 5.1).

Ultomiris is indicated in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab (see section 5.1).

4.2 Posology and method of administration
(…)

Posology
(…)
In aHUS, ravulizumab treatment to resolve TMA manifestations should be for a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. Patients who are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy (see section 4.4).

Special populations
(…)
Renal impairment
In aHUS clinical trials, patients with renal impairment including on dialysis were included.
(…)
Paediatric population
Paediatric patients with aHUS with body weight ≥ 40 kg are treated in accordance with the adult dosing recommendations. The weight-based doses and dosing intervals for paediatric patients ≥ 10 kg to < 40 kg is shown in Table 2.

Table 1: Ravulizumab weight-based dosing regimen for paediatric patient below 40 kg

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dosing interval
≥ 10 to < 20	600	600	Every 4 weeks
≥ 20 to < 30	900	2,100	Every 8 weeks
≥ 30 to < 40	1200	2,700	Every 8 weeks

*Maintenance dose is administered 2 weeks after loading dose

Data to support safety and efficacy of ravulizumab for patients with body weight below 10 kg are limited. Currently available data are described in section 4.8 but no recommendation on a posology can be made for patients below 10 kg body weight.
(…)

Method of administration
(…)
Table 3: Dose administration rate

Body weight range (kg)[a]	Loading dose (mg)	Minimum infusion duration minutes (hours)	Maintenance dose (mg)	Minimum infusion duration minutes (hours)
≥ 10 to < 20	600	113 (1.9)	600	113 (1.9)
≥ 20 to < 30	900	86 (1.5)	2,100	194 (3.3)
≥ 30 to < 40	1,200	77 (1.3)	2,700	167 (2.8)
≥ 40 to < 60	2,400	114 (1.9)	3,000	140 (2.4)
≥ 60 to < 100	2,700	102 (1.7)	3,300	120 (2.0)
≥ 100	3,000	108 (1.8)	3,600	132 (2.2)

[a] Body weight at time of treatment.
(…)

4.4 Special warnings and precautions for use
(…)

Immunization
Prior to initiating ravulizumab therapy, it is recommended that PNH and aHUS patients initiate immunizations according to current immunization guidelines.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH and aHUS, may experience increased signs and symptoms of their underlying disease, such as haemolysis. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Patients below the age of 18 years old must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations for each age group.
(…)

Infusion reactions
Administration of ravulizumab may result in infusion reactions. In clinical trials with PNH and aHUS, [(4 out of 296 in patients with PNH) and (4 of 89 patients with aHUS)] patients experienced infusion reactions which were mild in severity and transient [e.g., lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste)]. In case of infusion reaction, infusion of ravulizumab should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.
(…)

Treatment discontinuation for aHUS
There are no specific data on ravulizumab discontinuation. In a long-term prospective observational study, discontinuation of complement C5 inhibitor treatment (eculizumab) resulted in a 13.5-fold higher rate of TMA recurrence and showed a trend toward reduced renal function compared to patients who continued treatment.
If patients must discontinue treatment with ravulizumab, they should be monitored closely for signs and symptoms of TMA on an on-going basis. However, monitoring may be insufficient to predict or prevent severe TMA complications.
TMA complications post-discontinuation can be identified if any of the following is observed:
(i) At least two of the following laboratory results observed concurrently: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ravulizumab treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ravulizumab treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ravulizumab treatment (results should be confirmed by a second measurement)
Or
(ii) any one of the following symptoms of TMA: a change in mental status or seizures or other extra-renal TMA manifestations including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhoea; or thrombosis.
If TMA complications occur after ravulizumab discontinuation, consider reinitiation of ravulizumab treatment beginning with the loading dose and maintenance dose described in section 4.2

4.8 Undesirable effects

Summary of the safety profile
The most common adverse drug reactions ~~are upper respiratory trace infection~~ (very common frequency) are diarrhoea, nausea, vomiting, nasopharyngitis and headache. The most serious adverse reactions in patients in clinical trials are meningococcal infection and meningococcal sepsis (see section 4.4).
(…)

Description of selected adverse reactions
Meningococcal infection/sepsis
(…)
In aHUS studies, no meningococcal infections occurred among 89 patients receiving treatment with ravulizumab
(…)

Paediatric population
In paediatric patients with evidence of aHUS (aged 10 months to less than 18 years) included in ALXN1210-aHUS-312 study, the safety profile of ravulizumab appeared similar to that observed in adult

patients with evidence of aHUS. The safety profiles in the different paediatric subsets of age appear similar. The safety data for patient below 2 years of age is limited to four patients. The most common adverse reaction reported in paediatric patients was pyrexia.

The safety of ravulizumab in children with PNH aged 0 to < 18 years have not been established. No data are available.

6.6 Special precautions for disposal and other handling

(…)

Table 13: Loading dose administration reference table

Body weight range (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	900	90	90	180
≥ 30 to < 40	1200	120	120	240
≥ 40 to < 60	2,400	240	240	480
≥ 60 to < 100	2,700	270	270	540
≥ 100	3,000	300	300	600

[a] Body weight at time of treatment.

[b] Ultomiris should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

Table 14: Maintenance dose administration reference table

Body weight range (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	2100	210	210	420
≥ 30 to < 40	2700	270	270	540
≥ 40 to < 60	3,000	300	300	600
≥ 60 to < 100	3,300	330	330	660
≥ 100	3,600	360	360	720

[a] Body weight at time of treatment.

[b] Ultomiris should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

- העלון לרופא נשלח למשרד הבריאות לצורך העלאתו למאגר התרופות שבאתר משרד הבריאות.
- ניתן לקבל עלון זה מודפס על ידי פניה ישירה לבעל הרישום:

אלקסיון פארמה ישראל בע"מ, ת.ד. 7063, פתח תקווה 4917001.
טלפון: 03-9373753, פקס: 03-9373774

בברכה,
עוז וולך - רוקח ממונה
אלקסיון פארמה ישראל בע"מ